REMARKS

This Amendment responds to the Office Action mailed on April 1, 2009. In the Office Action, the Examiner:

- rejected claim 48 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement;
- rejected claims 1, 5, 11, 15, 22 and 41-47 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* (*Cancer Chemotherapy and Pharmacology* (2002) 50:237-242, "Tsimberidou *et al.*") in view of Man *et al.* (WO2001/34606, "Man *et al.*");
- rejected claims 3 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Alter *et al.* (*Blood* (1985) 66:373-379, "Alter *et al.*");
- rejected claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Canepa *et al.* (*British Journal of Haematology* (2001) 115:313-315, "Canepa *et al.*"); and
- rejected claims 48 and 49 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et. al.* and Vippagunta *et al.* (*Advanced Drug Delivery Reviews* (2001) 48:3-26, "Vippagunta *et al.*").

Claims 1, 3, 5-9, 11, 15, 22, and 41-51 were pending. Claims 50-51 were withdrawn from consideration by the Examiner. Claims 48-49 have been canceled without prejudice. Claims 1, 3 and 22 have been amended by deleting the terms "solvate or hydrate." No new matter is added by this Amendment. After this Amendment, the pending claims are 1, 3, 5-9, 11, 15, 22, and 41-47.

I. The Rejection of Claim 48 under 35 U.S.C. § 112, First Paragraph

On page 3 of the Office Action, the Examiner rejected claim 48 under 35 U.S.C. § 112 , first paragraph as allegedly failing to comply with the written description requirement. Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claim 48 has been canceled and therefore, the rejection is moot.

II. The Rejection of Claims 1, 5, 11, 15, 22 and 41-47 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 5 of the Office Action, the Examiner rejected claims 1, 5, 11, 15, 22 and 41-47 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* Applicant respectfully disagrees.

A. The cited references would not have provided any reason to combine their teachings because Etanercept and Compound A are not functional equivalents as alleged by the Examiner.

The Examiner alleged that Tsimberidou *et al.* teaches a method of treating agnogenic myeloid metaplasia (AMM) with Etanercept that inhibits TNF-α activity. *See* page 7 of the Office Action. The Examiner also alleged that Man *et al.* teaches that the instant claimed compound: {2-[(1 S)-I-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide ("**Compound A**") is a TNF-alpha inhibitor. *See* page 7 of the Office Action. The Examiner further alleged that it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (Etanercept) for another (Compound A) with an expectation of success, since the prior art establishes that both function in similar manner, thus resulting in the practice of claims 1, 5, 11, 15 and 22, with a reasonable expectation of success. *See* pages 7-8 of the Office Action.

Applicant submits that the Examiner has not established a *prima facie* case of obviousness because it would not have been *prima facie* obvious for a person of ordinary skill in the art to substitute Etanercept for Compound A with a reasonable expectation of success because Etanercept and Compound A do not function in similar manner and therefore, are not functional equivalents.

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on the mere fact that the components at issue are functional equivalents. *In re Scott*, 323 F.2d 1016, 139 USPQ 297 (CCPA 1963) (Components which are functionally or mechanically equivalent are not necessarily obvious in view of one another, and in this case, the use of a light wood or hardened foam resin core does not fairly suggest the use of a paper core.). The cited references fail to disclose functional equivalents as alleged by the PTO.

The Introduction section of Tsimberidou *et al.* at page 237-238 discloses that Etanercept inactivates TNF-α molecules by binding chemically to two free TNF-α molecules,

and thus blocks their interaction with cell surface TNF-α receptors. On the contrary, Man *et al.* discloses that to prevent excessive and unregulated TNF-α production, non-polypeptide isoindoline derivatives, such as Compound A, can be used to decrease the levels of TNF-α molecules. See page 1, lines 6-9 and 22-23 of Man *et al.* By decreasing the level of TNF-α, there is no need to inactivate the TNF-α molecules as taught by Tsimberidou *et al.* Therefore, it is not surprise to see that Man *et al.* does not disclose, teach or suggest inactivating the TNF-α molecule by binding them to Compound A. Further, as a matter of scientific fact, Compound A is incapable of binding to and thus inactivate TNF-α because the two TNF-α receptors are a 55-kDa and a 75-kDa protein and Compound A is not a protein at all, much less a protein with the appropriate molecular weight for binding.

In summary, Tsimberidou *et al.* and Man *et al.* teach that Compound A and Etanercept function in different manners. Therefore, a person of ordinary skill in the art would not have recognized that Etanercept and Compound A are functional equivalents. Therefore, it would not have been *prima facie* obvious for a person of ordinary skill in the art to substitute Etanercept for Compound A of the instant claims.

B. Tsimberidou *et al.* teaches away from the claimed invention.

The Patent Office alleges that (1) Tsimberidou *et al.* states that current treatments other than: allogenic stem cell transplantation, including hydroxyurea, alpha-interferon, androgens, thalidomide, and splenectomy are ultimately ineffective in AMM patients; and (2) the phrase "other than" means that the treatments and compounds cited after the phrase, but nothing else, are effective against AMM. *See* Office Action, page 10. This allegation by the Patent Office in itself supports that Tsimberidou *et al.* teaches away from the claimed invention because Compound A of the instant claims is not one of the cited compounds after the phrase "other than" and therefore, Tsimberidou *et al.* teaches that Compound A is not effective against AMM. Further, Tsimberidou *et al.* is silent as to the claimed methods using the recited Compound A in treating MPD. Tsimberidou *et al.* does not disclose or suggest anything about the use of Compound A recited in the instant claims for treating MPD. In summary, Tsimberidou *et al.* teaches away from the claimed invention. For purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. "[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). (Emphasis added.)

C. No reasonable expectation of success exists in combining Tsimberidou *et al.* and Man *et al.* as required to arrive at the claimed methods.

Further, the Patent Office has not presented evidence to demonstrate that the specific compound of the claimed methods would be effective in treating myeloproliferative disease (MPD). Without such evidence, no reasonable expectation of success exists because a reasonable expectation of success requires more than a motivation to simply "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result...." *Medichem v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); *see also KSR*, 127 S.Ct. at 1739 and 1742 (an obviousness determination takes into account whether the combination of elements would yield "anticipated success" or "predictable results"). Furthermore, the courts have long recognized the unpredictability of the biological properties of chemical compounds. *See, e.g., In re Eli Lilly & Co.*, 902 F.2d. 943, 948 (Fed. Cir. 1990) ("we recognize and give weight to the unpredictability of biological properties..."). In view of this knowledge, even if Tsimberidou *et al.* teaches that inhibition of TNF-α could be useful in treating AMM as alleged by the PTO, one of ordinary skill in the art would not expect that every compound demonstrating TNF-α activity would be useful in treating AMM or MPD. Without more specific guidance in the art, no reasonable expectation exists to use the specific compound of the instant methods for the treatment of MPD. Thus, because the Patent Office has not presented sufficient evidence of a reasonable expectation of success, a *prima facie* case of obviousness has not been made.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 1, 5, 11, 15, 22 and 41-47 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.*

III. The Rejection of Claims 3 and 7-9 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 10 of the Office Action, the Examiner maintained the rejection of claims 3 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* as applied to claims 1, 5, 11, 15, 22 and 41-47 above, and further in view of Alter *et al.* Applicant respectfully disagrees.

Claim 3 recites all recitations of claim 1 plus the recitation of "and a therapeutically or prophylactically effective amount of at least one second active agent." Since claim 1 is not

obvious over Tsimberidou *et al.* in view of Man *et al.* for the reasons discussed above, claim 3 and claims 7-9, which depend on claim 3 directly or indirectly, are also not obvious over Tsimberidou *et al.* in view of Man *et al.* Alter *et al.* merely discloses treating patients with myeloproliferative syndromes with hydroxyurea, but it does not disclose, teach or suggest treating or managing a MPD with Compound A, much less in combination with at least one second active agent. The PTO has failed to establish the obviousness of the instant claims because it failed to establish that each of claim limitations is taught or suggested in the prior art, as required for a *prima facie* case of obviousness. *See, e.g. In re Ochiai*, 71 F.3d 1565, 1572. (Fed. Cir. 1995) (PTO must establish "that the invention as claimed in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations."). Therefore, Tsimberidou *et al.*, Man *et al.* and Alter *et al.*, individually or in combination, does not disclose, teach or suggest all recitations of claim 3 and claims 7-9, particularly treating or managing a MPD with Compound A and a second active agent.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claims 3 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Alter *et al.*

IV. The Rejection of Claims 6 under 35 U.S.C. § 103(a) Should Be Withdrawn

On page 11 of the Office Action, the Examiner maintained the rejection of claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* as applied to claims 1, 5, 11, 15, 22 and 41-47 above, and further in view of Canepa *et al.*. The Examiner alleged that claims 14 and 15 were rejected in the Office Action mailed on November 12, 2008 (*see* page 10). Applicant respectfully disagrees.

Claim 6 depends on claim 1 or 3. Since claim 1 or 3 is not obvious over Tsimberidou *et al.* in view of Man *et al.* for the reasons discussed above, claim 6 is also not obvious over Tsimberidou *et al.* in view of Man *et al.* Canepa *et al.* merely discloses the treatment of MPD with thalidomide but it does not disclose, teach or suggest treating or managing a MPD with Compound A. Therefore, Tsimberidou *et al.*, Man *et al.* and Canepa *et al.*, individually or in combination, does not disclose, teach or suggest all recitations of claim 6, particularly administering Compound A for treating or managing a MPD patient who is refractory to a prior thalidomide treatment.

In view of the foregoing, Applicant respectfully requests withdrawal of the rejection of claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* and Canepa *et al.*

V. The Rejections of Claims 48 and 49 under 35 U.S.C. § 103(a)

On page 12 of the Office Action, the Examiner rejected claims 48 and 49 under 35 U.S.C. § 103(a) as being unpatentable over Tsimberidou *et al.* in view of Man *et al.* as applied to claims 1, 5, 11, 15, 22 and 41-47 above, and further in view of Vippagunta *et al.* Solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, claims 48 and 49 have been canceled and therefore, the rejection is moot.

CONCLUSION

In light of the above amendments and remarks, the Applicant respectfully requests that the Examiner reconsider this application with a view towards allowance.

No fee is believed due for this submission. However, if any fees are required for the entry of this paper or to avoid abandonment of this application, please charge the required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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/Kam W. Law/

by: Kam W. Law — Reg. No. 44,205
For: Anthony M. Insogna — (Reg. No. 35,203)

Jones Day
222 East 41st Street
New York, N.Y. 10017-6702
Tel: 212-326-3778